Clinical Significance of an Impaired Mononuclear Phagocyte System Immune Clearance in Human Nephritis

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Dear Sir,

Experimental models [1] suggest a critical role of the mononuclear phagocyte system (MPS) in the removal of immunologically active substances.

The application of widely accepted techniques [2] to the study of the MPS function in immunologically mediated glomerulonephritis (GN) has provided a major step in understanding the pathogenesis of these diseases. However, conflicting results have been obtained even by using the same methodological approaches in similar samples of patients, making difficult to derive definitive conclusions for clinical purposes.

To assess the prevalence and the clinical significance of a defective MPS function, we have reexamined our own four-year experience in detecting the splenic MPS immune clearance of IgG-sensitized 51Cr-labelled auto-logous red blood cells (RBC) [3] in patients with biopsy-proven GN.

Patients included 17 cases of lupus nephritis, 10 of cryoglobulinaemia-associated GN, 6 of systemic vasculitis-associated GN, 9 Henoch-Schönlein, 1 of vascular amyloidosis, 28 of membranous GN, 10 of membranoproliferative GN, 33 of primary IgA nephropathy, 10 of focal and segmental glomerulosclerosis, 5 of IgM mesangial GN, 1 of rapidly progressive postinfectious GN. Among the 43 patients with multisystem disorders with renal involvement, 29 cases with obvious urinary abnormalities (> 1.5 g proteinuria/day and > 15 RBC/high-power microscopic field) associated with at least two systemic signs were found to have a prolongation of MPS immune clearance as compared to those with minimal urinary abnormalities (< 0.7 g proteinuria/day and < 5 RBC/high-power microscopic field) without systemic manifestations ($p < 0.05$). In the lupus subgroup the MPS impairment was found to be related ($p < 0.05$) to the levels of IgG immune complexes detected by the Clq solid-phase test [4]. Moreover among the 87 patients with primary GN, 69 cases with obvious urinary abnormalities (as defined above) were found to have a significant decrease in MPS function as compared to those with minimal or no urinary signs ($p < 0.02$). This relationship was particularly strong ($p < 0.01$) in primary IgA nephropathy (32 cases), in which MPS dysfunction and IgA immune complex levels, detected by the conglutinin solid phase test [5], were

significantly related ($p < 0.01$). Follow-up assessment in 23 primary or secondary GN patients showed changes in MPS status associated with concordant changes in clinical and urinary activity in all but 2 cases.

The MPS clearance function was not related to the duration of disease, antecedent treatment, or any of the HLA-A, B, C, DR, DQ antigens (detected in 87 cases). Eight HLA-DR2 and even 26 DR3-positive patients, supposed to have a primary impairment of macrophage function [6], were found to be randomly distributed between the groups with or without defective MPS clearance. The absence of correlation was particularly obvious among 26 patients with idiopathic membranous nephropathy, in whom HLA typing revealed a statistically significant increase in HLA-DR3 antigen with a relative risk of 7.6 ($p = 0.00056$).

Twelve patients, consecutively treated with plasma exchange associated with steroid and immunosuppressive drugs, were analysed before and after 4–5 weeks of treatment. In Vn cases (1 lupus nephritis, 2 systemic vasculitis, 1 Henoch-Schönlein syndrome, 2 primary IgA GN, 1 crescentic acute GN) an improvement in MPS immune clearance paralleled a clinical amelioration. In 2 cases (1 lupus nephritis and 1 primary IgA GN) who had a clinical improvement after PE, the MPS function was normal before and remained unchanged after the treatment. The other 3 patients, who had prolonged MPS clearance, did not show the expected reversal of the

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macrophage impairment nor any clinical benefit for this treatment. They included a HLA-B8, DR3-positive patient with primary IgA GN and 2 DR3-negative patients with systemic vasculitis and essential cryoglobulinaemia, respectively, who both underwent chronic haemodialysis. It follows from these data that more than half of the primary and the majority of the secondary GN patients with obvious urinary abnormalities have a defective MPS clearance. A genetically mediated MPS impairment does exist only in a very few cases, but the genetic influence is not generally a major determinant. PE therapy improves the MPS clearance in a considerable number of patients, but not in every case. The lack of reversal of this dysfunction indicates fewer chances of clinical remission.

The biological significance of an impaired immune clearance as assessed *in vivo* by evaluating the macrophage removal of IgG-sensitized RBC is intriguing. The defect is surely dynamic and, in the cases sequentially studied, follows, to a great extent, the magnitude of the urinary abnormalities. It could be speculated that this dysfunction represents a general impairment in removal of immune substances, which promotes their glomerular deposition. However it is difficult to accept that the IgG-coated RBC test probe exactly reflects the behaviour of the diverse immune materials involved in the pathogenesis of different GN. Moreover it cannot be denied that it still remains to be established whether the MPS dysfunction favours the disease rather than the reverse.

Nevertheless, on the basis of our own experience, which represents one of the widest in the literature, MPS function evaluation can be considered a valuable tool for the immunological monitoring of GN patients.

Acknowledgments

The HLA typing was performed by Dr. A. Amoroso, Centro Immunogenetica ed Istocompatibilità, Torino.

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